Decreased Serum Concentrations of 1,25(OH)$_2$-Vitamin D$_3$ in Patients With Gout

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We measured serum concentrations of 1,25(OH)$_2$-vitamin D$_3$, 25(OH)-vitamin D$_3$, parathyroid hormone (PTH), and uric acid in 114 male patients with primary gout and 51 normal male control subjects. Serum 1,25(OH)$_2$-vitamin D$_3$ was significantly lower in patients with gout compared with control subjects (38.4 ± 11.9 *v* 44.4 ± 11.0 pg/mL, $P < .005$), whereas no differences were observed between the two groups for serum 25(OH)-vitamin D$_3$ or PTH. Serum uric acid was significantly higher in patients with gout versus control subjects (8.8 ± 1.3 *v* 5.7 ± 1.0 mg/dL, $P < .0001$). In addition, there was a significant negative correlation between serum uric acid and 1,25(OH)$_2$-vitamin D$_3$ concentrations ($r - .17$, $P < .05$). Administration of allopurinol or benzbromarone to the patients for 1 year caused a significant increase in serum 1,25(OH)$_2$-vitamin D$_3$, which was associated with a significant decrease in serum uric acid. In contrast, serum concentrations of 25(OH)-vitamin D$_3$ and PTH were not affected by these drugs. These results suggest that uric acid per se may directly decrease serum 1,25(OH)$_2$-vitamin D$_3$ in patients with gout by inhibiting 1α-hydroxylase activity.

IT IS WIDELY ACCEPTED that the major biologic role of vitamin D in mammals is the regulation of mineral homeostasis and parathyroid hormone (PTH) secretion.[1,2] However, it has been recently reported that purine derivatives suppress 1,25-dihydroxycholecalciferol (1,25(OH)$_2$-vitamin D$_3$) synthesis in patients with renal failure and hyperuricemia[3] and that the serum active vitamin D level was inversely related to the serum uric acid,[4] suggesting a possible relationship between vitamin D and uric acid. A previous study demonstrated that uric acid decreases plasma 1,25(OH)$_2$-vitamin D$_3$.[5] However, the effect of uric acid on vitamin D metabolismin in patients with gout, who have hyperuricemia, remains to be clarified. Therefore, we determined the plasma concentrations of 1,25(OH)$_2$-vitamin D$_3$, 25(OH)-vitamin D$_3$, and PTH in patients with gout. We also examined the effect of a decrease in plasma uric acid by allopurinol, a xanthine oxidase inhibitor, or benzbromarone, a uricosuric agent, on the plasma concentration of 1,25(OH)$_2$-vitamin D$_3$ in patients with gout.

SUBJECTS

Subjects and Sample Collection

The subjects were 114 male patients with primary gout aged 47.5 ± 11.3 years who fulfilled at least six of 12 clinical, laboratory, and radiographic criteria as outlined by the American Rheumatism Association[6] and 51 healthy male subjects aged 45.2 ± 11.1 years who were randomly selected from applicants undergoing an annual health examination. The control subjects were judged to be normal by physical examination and medical history and in terms of the serum uric acid concentration, fasting blood sugar level, and renal and hepatic function tests. After informed consent, any medication known to affect the serum uric acid concentration or vitamin D metabolism was withheld for at least 1 month before the study.

The study was performed from July through August 1995 and from July through August 1996 to minimize any seasonal changes in vitamin D levels.[7,8] All sample collections were performed on an outpatient basis. During the study, all subjects were ambulatory and on their usual diet, and no instructions on dietary or fluid intake were given. Blood samples were drawn after an overnight fast, and the serum was separated for determination of 1,25(OH)$_2$-vitamin D$_3$, 25(OH)-vitamin D$_3$, PTH, and uric acid concentrations and other biochemical variables. In addition, 24-hour urine samples were collected for determination of the urinary excretion of uric acid, calcium, and phosphate. After determining uric acid metabolism in the patients, allopurinol (100 to 200 mg/d) or benzbromarone (25 to 50 mg/d) were administered to 46 patients with uric acid excretion greater than 800 mg/d in urine and 23 patients with uric acid clearance less than 6 mL/min, respectively. Serum concentrations of uric acid, 1,25(OH)$_2$-vitamin D$_3$, 25(OH)-vitamin D$_3$, and PTH were measured before and 1 year after the patients received uric acid–lowering agents.

Analytical Techniques

The serum uric acid concentration was measured by the uricase method using automated analysis. The 1,25(OH)$_2$-vitamin D$_3$ level was measured by a radioreceptor assay using a 1,25(OH)$_2$-vitamin D$_3$ kit (SRL; Yamasa, Tokyo, Japan). The 25(OH)-vitamin D$_3$ concentration was determined by a competitive protein-binding assay using diluted rat serum. The PTH concentration was determined by a radioimmunoassay specific for the midregion of the PTH molecule, consisting of PTH antiserum (CH9), ^{125}I-labeled Tyr^{42}hPTH(43-68), and synthetic hPTH(1-84) as the standard (Yamasa).

Statistical Methods

Data are expressed as the mean ± SD. Observed differences were tested by Student's *t* test for significance. Comparisons of serum uric acid and 1,25(OH)$_2$-vitamin D$_3$ levels before and after uric acid–lowering therapy were assessed by the two-tailed paired *t* test. A *P* value less than .05 was considered significant.

RESULTS

Clinical features and laboratory data of the subjects are shown in Table 1. The age, body mass index, and alcohol intake were similar in gout and control subjects (47.5 ± 11.3 *v* 45.2 ± 11.1 years, 24.8 ± 3.4 *v* 24.0 ± 2.7 kg/m^2, and 29.6 ± 28.7 *v* 21.7 ± 21.7 g/d, respectively). Serum uric acid was significantly higher in patients with gout than in the control subjects (8.8 ± 1.3 *v* 5.7 ± 1.0 mg/dL, $P < .0001$). Serum 1,25(OH)$_2$-vitamin D$_3$ was significantly lower in patients with gout than in the control subjects (38.4 ± 11.9 *v* 44.4 ± 11.0 pg/mL, $P < .005$). However, 25(OH)-vitamin D$_3$ and PTH serum values were not different between the two groups (25.5 ± 6.2 *v* 23.6 ± 6.8 ng/mL and 361.3 ± 117.6 *v* 349.2 ± 110.5 pg/mL, respectively). Despite a difference in the

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Table 1. Clinical and Laboratory Features of the Subjects

Parameter	Gout Patients (n = 114)	Controls (n = 51)	P
Age (yr)	47.5 ± 11.3	45.2 ± 11.1	NS
BMI (kg/m^2)	24.8 ± 3.4	24.0 ± 2.7	NS
Alcohol intake (g/d)	29.6 ± 28.7	21.7 ± 21.7	NS
Serum uric acid (mg/dL)	8.8 ± 1.3	5.7 ± 1.0	<.0001
Serum creatinine (mg/dL)	0.86 ± 0.18	0.86 ± 0.11	NS
Serum calcium (mg/dL)	9.8 ± 0.3	9.8 ± 0.2	NS
Serum phosphate (mg/dL)	3.0 ± 0.4	3.0 ± 0.5	NS
$1,25(OH)_2D_3$ (pg/mL)	38.4 ± 11.9	44.4 ± 11.0	<.005
$25(OH)D_3$ (ng/mL)	25.5 ± 6.2	23.6 ± 6.8	NS
PTH (pg/mL)	361.3 ± 117.6	349.2 ± 110.5	NS

NOTE. Data are expressed as the mean ± SD.

Abbreviations: BMI, body mass index; $1,25(OH)_2D_3$, $1,25(OH)_2$-vitamin D_3; $25(OH)D_3$, 25(OH)-vitamin D_3.

serum $1,25(OH)_2$-vitamin D_3 concentration, serum concentrations of calcium and phosphate were not different between the two groups (Ca, 9.8 ± 0.3 *v* 9.8 ± 0.2 mg/dL; phosphate, 3.0 ± 0.4 *v* 3.0 ± 0.5 mg/dL). Administration of allopurinol or benzbromarone caused a significant increase in serum $1,25(OH)_2$-vitamin D_3 (from 34.5 ± 9.2 to 42.1 ± 13.1 pg/mL with allopurinol and from 38.8 ± 11.4 to 43.6 ± 12.5 pg/mL with benzbromarone, $P < .0001$ and $P < .05$, respectively), which was associated with a significant reduction in the serum uric acid level (from 8.7 ± 1.3 to 6.0 ± 1.0 mg/dL with allopurinol and from 9.2 ± 1.2 to 5.2 ± 1.1 mg/dL with benzbromarone, $P < .0001$ and $P < .0001$; Fig 1A and B). However, neither agent changed the serum concentration of 25(OH)-vitamin D_3 (from 26.3 ± 5.6 to 27.5 ± 5.7 ng/mL with allopurinol and from 26.1 ± 6.5 to 26.5 ± 7.8 ng/mL with benzbromarone, nonsignificant [NS]) and PTH (from 363.5 ± 131.8 to 359.8 ± 131.5 pg/mL with allopurinol and from 347.7 ± 109.8 to 354.1 ± 113.0 pg/mL with benzbromarone, NS). The urinary excretion and serum concentration of calcium and phosphate were not affected by administration of allopurinol or benzbromarone (data not shown).

DISCUSSION

A previous study found that $1,25(OH)_2$-vitamin D_3 metabolism is suppressed in uremic patients.[3] Later, it was determined that the substances responsible for the decreased concentration of $1,25(OH)_2$-vitamin D_3 in the serum of uremic patients were purine derivatives such as uric acid and xanthine.[5] Vanholder et al[3] reported that allopurinol, a xanthine oxidase inhibitor, increased the plasma concentration of 25(OH)-vitamin D_3, with a concomitant decrease in the serum uric acid concentration, but did not change the plasma concentrations of creatinine, calcium, phosphorus, PTH, and $1,25(OH)_2$-vitamin D_3 in patients with renal failure and hyperuricemia. These results suggest that the decrease in $1,25(OH)_2$-vitamin D_3 is attributable to the elevated uric acid concentration in these subjects. However, the effect of uric acid on $1,25(OH)_2$-vitamin D_3 metabolism in patients with hyperuricemia and normal renal function remains unclear. Therefore, we performed the present study using patients with gout as subjects.

The present study demonstrated that serum $1,25(OH)_2$-vitamin D_3 was significantly lower in patients with gout, in whom the serum uric acid was significantly higher than the level in the control subjects, but that serum 25(OH)-vitamin D_3 and PTH levels were not different between the two groups. Hsu et al[5] have demonstrated that the rate of $1,25(OH)_2$-vitamin D_3 production decreased with a reduction in renal 1α-hydroxylase activity by increasing the plasma uric acid concentration after infusion of sodium urate. It has also been reported that allopurinol did not change the $1,25(OH)_2$-vitamin D_3 clearance

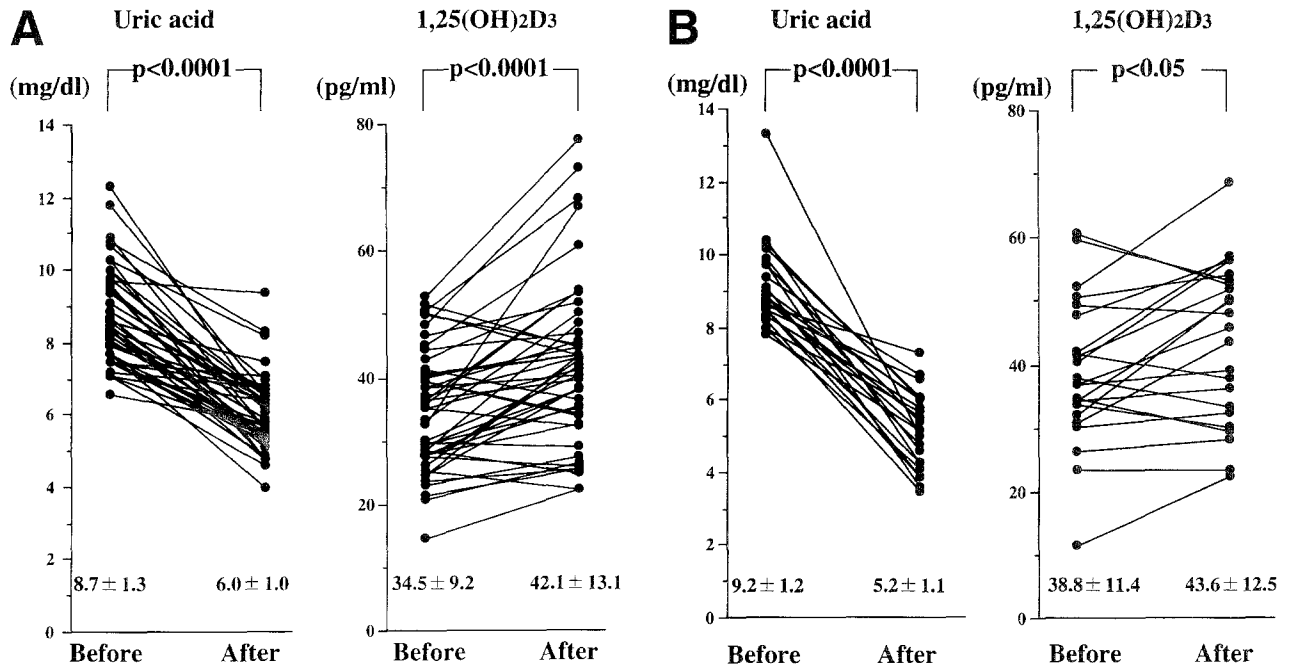

Fig 1. Changes in serum uric acid and $1,25(OH)_2$-vitamin D_3 levels in gout patients after therapy. (A) Allopurinol; (B) benzbromarone. Serum $1,25(OH)_2$-vitamin D_3 levels were significantly increased and were associated with a decrease in uric acid after both treatments.

rate or its rate of production in normal rats.[3] Therefore, allopurinol does not seem to affect 1α-hydroxylase activity directly in humans. By inhibiting xanthine oxidase activity, allopurinol increases the xanthine concentration, which also suppresses 1α-hydroxylase activity, as does uric acid. However, the increase in serum xanthine is small compared with the decrease in serum uric acid by allopurinol,[9] and the net effect is thereby an increase in the serum $1,25(OH)_2$-vitamin D_3 concentration. We administered a moderate dose of allopurinol to 46 patients and benzbromarone to 23 patients for 1 year, and found a significant increase in $1,25(OH)_2$-vitamin D_3 associated with a reduction in serum uric acid after both treatments. Thus, irrespective of the mode of action of the uric acid–lowering agent, a significant increase in serum $1,25(OH)_2$-vitamin D_3 was observed. A previous study demonstrated an increase in PTH levels after long-term (12 to 24 months) administration of allopurinol to patients with recurrent renal calcium stones.[10] However, in the present study, no significant changes in PTH or 25(OH)-vitamin D_3 serum levels were observed after 1 year of allopurinol therapy. A possible relationship between renal hypouricemia due to defective uric acid transport in the renal tubules and a high serum concentration of $1,25(OH)_2$-vitamin D_3 has been suggested.[11] However, in our study, it seems unlikely that a decreased uric acid clearance in patients with gout is responsible for the low serum concentration of $1,25(OH)_2$-vitamin D_3, since serum $1,25(OH)_2$-vitamin D_3 is decreased in gout patients with normal uric acid clearance. Furthermore, the serum levels of $1,25(OH)_2$-vitamin D_3 were not different between the underexcretors of uric acid receiving benzbromarone and overexcretors receiving allopurinol. In addition, there was a significant negative correlation between serum uric acid and $1,25(OH)_2$-vitamin D_3 concentrations ($r = .17$, $P < .05$). Therefore, it is conceivable that uric acid itself decreases the serum concentration of $1,25(OH)_2$-vitamin D_3 in patients with gout, although the effect of benzbromarone on 1α-hydroxylase activity cannot be completely excluded. The serum concentration of $1,25(OH)_2$-vitamin D_3 was much higher in patients with gout than in patients with renal insufficiency despite the much higher serum concentration of uric acid. Therefore, some unknown factor(s) other than uric acid may contribute to the decrease in serum $1,25(OH)_2$-vitamin D_3.[12]

The most important clinical manifestations of vitamin D deficiency are related to the development of renal osteodystrophy, rickets in children, and secondary hyperparathyroidism. However, to our knowledge, there have been no studies suggesting a high incidence of osteoporosis in patients with gout. Furthermore, the serum $1,25(OH)_2$-vitamin D_3 concentration was not markedly decreased in patients with gout versus patients with renal insufficiency (38.4 ± 11.9 pg/mL in our study v 30.8 ± 2.7 pg/mL in nine patients with renal insufficiency in the study by Vanholder et al[3]), in whom osteodystrophy is frequently observed due to a derangement of vitamin D metabolism. In addition, the plasma concentration and urinary excretion of calcium and phosphate did not change with administration of allopurinol or benzbromarone. Therefore, the decrease in serum $1,25(OH)_2$-vitamin D_3 in patients with gout may not be clinically important in this regard.

However, recently, evidence has been accumulating that vitamin D metabolism is related to diabetes mellitus, impaired glucose tolerance,[7] obesity,[13,14] and hypertension,[15,16] all of which are common in patients with gout. In addition, a previous study suggested that reduced $1,25(OH)_2$-vitamin D_3 levels are associated with increases in blood pressure and triglyceride, as well as impaired glucose tolerance,[4] which are elements of the metabolic syndrome X. Therefore, further studies are required to clarify the association, if any, between $1,25(OH)_2$-vitamin D_3 levels and hypertension, hypertriglyceridemia, obesity, and impaired glucose tolerance in patients with gout.

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